Protocol A3921145

A LONG-TERM, OPEN-LABEL FOLLOW-UP STUDY OF TOFACITINIB FOR TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS (JIA)

Statistical Analysis Plan
(SAP)

Version: 4

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Associated Protocol Amendment	Change	Rationale
4 (26-Jan-2024)	Protocol Amendment 12 (06-May-2022)	Section 3.4.1: clarified that enrollment gap refers to the number of off-study days	For clarification
		Section 3.4.2: added additional baseline summaries for subjects with sJIA.	To provide summaries of baseline disease characteristics specific to sJIA subjects.
		Section 6.7: added an end date for COVID-19 pandemic	To add an end date for COVID-19 pandemic related periods in analyses
		Section 7: added that IA may be performed for purposes of planned publications.	Clarifies that IA is allowed for planned publications (consistent with protocol amendment 12)
		Appendix 1.7: Updated the description of how cutoff values of JADAS-27 disease activities for polyarthritis and oligoarthritis will be applied to sJIA subjects.	For sJIA subjects, the cutoff values will be based on number of active joints at baseline.
		Other updates in Sections 2, 6.2 and Appendix 1.5.	Minor corrections and clarifications for consistency.
3 (31-Aug-2021)	Protocol Amendment 11 (26-May-2021)	Section 2.2: protocol languages were updated.	To be consistent with protocol amendment 11.
		Section 3.4.1: updated baseline definition.	To clarify how to determine baseline values in various scenarios.
		Section 3.4.2: added a subsection to list all baseline disease characteristics.	To clarify what baseline disease characteristics will be summarized.
		Section 4.4: updated analysis set definitions	To add an additional analysis set for sJIA subjects from index study A3921165 alone.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Associated Protocol Amendment	Change	Rationale
			To clarify definition of pJIA analysis set.
		Section 5.3: updated missing data handling method.	To add missing data handling method for Tanner Stage assessment.
		Sections 6.1, 6.2, 6.5, 6.6: details were added for efficacy analyses, baseline summaries and safety analyses.	To clarify how the analyses will be performed.
		Section 6.2.1: supportive analyses were added to evaluate the impact of expired/non-standard ESR kits.	To address the impact of expired/non-standard ESR kits.
		Section 6.4: removed subset analysis by tofacitinib dose group for sJIA subjects.	Tofacitinib 10 mg BID dose group has been removed from the protocol.
		Section 6.7: a new section was added for additional analyses to address COVID-19 pandemic impacts.	To address COVID-19 pandemic impacts.
		Section 8: a new section was added for references.	To list references for endpoint derivation details.
		Appendix 1.2: a new appendix was added for JIA joint count derivations.	To clarify the derivation method for JIA joint counts.
		Appendix 1.3, 1.4, 1.5, 1.6, 1.7, 1.9, 1.10: updated details in efficacy endpoint calculations.	To make sure endpoints will be calculated correctly.
		Appendix 1.11: Added analysis windows for Tanner Stage.	To add analysis windows for Tanner Stage.
		Other updates in Sections 3.1, 3.2, 4, and Appendix 1.1.	Minor corrections and clarifications for consistency.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Associated Protocol Amendment	Change	Rationale
2.0 (31-Oct-2017)	Protocol Amendment 7 (10-Aug-2017)	SAP template was updated to the newest one dated 30-Jun-2015.	To align with SOP.
		Section 2, 2.1 and 2.2: Protocol languages were updated.	To be consistent with protocol amendment 7.
		Section 3: Endpoints were updated according to protocol amendment 7, and definition of baseline variables was added.	To be consistent with protocol amendment 7.
		Section 4: Four more analysis sets were added: sJIA analysis set, pJIA analysis set, ERA analysis set and PsA analysis set.	To analyze sJIA, pJIA, ERA and PsA subjects separately.
		Section 6.1 and 6.2: Detailed LDL-C summarization was added; change analysis from by qualifying/index study to by JIA subtype; stratification by baseline weight was deleted.	LDL-C need to be reported separately for direct and indirect method; analyze by JIA subtype rather than by index study can represent subject population better; stratification by baseline weight is no longer needed.
		Section 6.4: subgroup analysis by dose group was added for sJIA subjects.	To investigate impact of dose level for sJIA subjects.
		Appendix 1.1 to 1.10: added detailed endpoint calculation.	To make sure programming team calculate the endpoints correctly.
		Appendix 1.11: revised visit window.	To be consistent with schedule of activities in protocol amendment 7.
1 (12-Apr-2012)	Original (16-Nov-2011)	Not Applicable	Not Applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study A3921145. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Tofacitinib (also known as CP-690,550) is currently approved in the United States and more than 98 countries for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. In adults, it is also approved for the treatment of psoriatic arthritis (PsA), ulcerative colitis and ankylosing spondylitis. It may be used in combination with methotrexate or other non biologic disease modifying antirheumatic drugs (DMARDs). In the pediatric population, from 2 to less than 18 years of age, tofacitinib is approved for active polyarticular course JIA in the United States and polyarticular JIA and juvenile PsA in the EU.

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays tofacitinib, inhibits JAK1, JAK2, JAK3, to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukins (IL) IL-2, -4, -7, -9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and IFN γ. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

The tofacitinib pediatric development program is designed to demonstrate both efficacy, as demonstrated by a reduction in signs and symptoms of JIA in subjects 2 years of age and older, and safety supporting the use of tofacitinib for the treatment of pediatric subjects with JIA.

The rationale of this study is to enable subjects potentially benefitting from treatment in a previous qualifying/index study to continue to receive tofacitinib at the same dose as the qualifying/index study (unless further analysis of the qualifying/index study data indicate otherwise), and to characterize long-term safety and tolerability of tofacitinib for the treatment of JIA.

It is anticipated that benefit of continued treatment with tofacitinib for individual subjects in this study will have been established in the qualifying/index study as per the Investigator's assessment. Potential risks of continued treatment are expected to be consistent with those described in the Single Reference Safety Document (current version of the tofacitinib Investigator Brochure).

2.1. Study Objectives

2.1.1. Primary

- The primary objective of this study is to determine the long-term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA.

2.1.2. Secondary

- The secondary objective of this study is to evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.

2.1.3. Exploratory

The exploratory objectives of this study are:

- To assess tofacitinib pharmacokinetics (PK) in pediatric subjects on a stable dose of tofacitinib in the setting of a long-term, open label study.

- To assess changes in PK parameters (within subject) with increase in weight in this pediatric population and to explore exposure-response relationships of tofacitinib for various efficacy and safety endpoints after long term exposure of tofacitinib in this pediatric population.

2.2. Study Design

This is a Phase 2/3, long term, open-label, follow-up study. Subjects will have previously participated in qualifying/index study in the tofacitinib JIA program. Those who have already completed such participation and enroll outside the 14-day window following completion of the End of Study (EOS) Visit of the qualifying/index study will participate in a Screening Visit to determine eligibility. A Baseline Visit will then occur within 28 days after the Screening Visit. For subjects who are completing participation in a qualifying study of tofacitinib and enrolling on the same day of the EOS Visit of the qualifying/index study, the EOS Visit of the qualifying/index study can be combined with the Screening and Baseline Visits for this study. The subjects who enroll within the 14-day window following completion of the EOS Visit of the qualifying/index study will participate in a combined Screening and Baseline Visit for this study. After the Baseline Visit, visits will occur at 1 month (1 month=30 days) and 3 months, then every 3 months thereafter as long as the subject remains in the study.

Approximately 340 participants are projected to enroll into this open label extension study after completing a qualifying/index study (i.e., A3921103, A3921104 or A3921165) in the JIA program.

For subjects who entered this study from the A3921103 and A3921104 qualifying/index studies, their participation in this study ends after the first global marketing approval of tofacitinib for the treatment of polyarticular course Juvenile Idiopathic Arthritis (pJIA) in any country.

This study will end once the last subject, and all other subjects, who entered from study A3921165 have completed approximately 1 year in this study, or after the first marketing approval of tofacitinib for the treatment of systemic JIA, whichever comes first.

The total duration of an individual subject's participation may vary depending upon when they entered the trial.

Applicable to Canadian Investigator Sites Only: The duration of subject participation will be restricted to 3 years, unless, in the Investigator's opinion, it is in the subject's best interest to continue receiving tofacitinib (to be determined on a case-by-case basis and in consultation with the Sponsor).

Depending on local regulatory requirements, and as per the EU Voluntary Harmonisation Procedure (EU VHP), access to tofacitinib may be made available to patients after the conclusion of this study via, but not limited to, an expanded access/compassionate use program until either 1) commercially available for JIA; 2) no longer beneficial to a patient as determined by the treating investigator; 3) the benefit-risk for JIA is determined to be unfavorable; or 4) the sponsor's application for marketing authorization is denied/disapproved for any reason by both US FDA and EMA.

The Sponsor may continue to provide tofacitinib to patients benefitting from this treatment in situations where the patient cannot access treatment through typical post-approval channels. Availability of the oral solution formulation may be limited or discontinued when patients taking the oral solution have either discontinued treatment or have transitioned to use of the oral tablet formulation consistent with applicable weight-based dosing guidance.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Incidence of clinical laboratory abnormalities and change from baseline in clinical laboratory values;
- Incidence and severity of adverse events;
- Validated assessments of growth (body weight and height) and pubertal development (Tanner Stage of Development);
- Incidence of abnormalities in physical examination;
- Incidence of vital sign abnormalities and change from baseline in vital sign measures;

3.2. Secondary Endpoints

The following efficacy parameters will be assessed:

- Change from baseline in physician global evaluation of disease activity at each visit.
- Change from baseline in number of joints with active arthritis at each visit.

- Change from baseline in number of joints with limitation of motion at each visit.
- Change from baseline in index of inflammation (C-reactive protein [CRP] and Erythrocyte Sedimentation Rate [ESR]) at each visit.
- Childhood Health Assessment Questionnaire (CHAQ) at each visit:
    - Change from baseline in Parent's Assessment of Physical Function (CHAQ Disability Index).
    - Change from baseline in Parent's Assessment of Child's Arthritis Pain (CHAQ Discomfort Index, Visual Analog Scale [VAS]).
    - Change from baseline in Parent's Global Assessment of Overall Wellbeing (CHAQ subsection, Visual Analog Scale [VAS]).
- JIA American College of Rheumatology (ACR) response at each visit.
- Occurrence of JIA ACR disease flare at each visit after Month 3.
- JIA ACR Clinical Inactive Disease status at each visit, and clinical remission at each visit after 24 weeks since study start. Note that clinical remission is counted as 6 months (24 weeks) of inactive disease during study, and 24 weeks will be used in programming.
- Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 27 CRP and JADAS-27 ESR, and occurrence of JADAS minimum disease activity and inactive disease at each visit.
- Achieving eligibility of tapering for corticosteroids, methotrexate (MTX)/leflunomide, and tofacitinib, respectively.
- Achieving partial tapering success for corticosteroids, MTX/leflunomide, and tofacitinib, respectively.
- Achieving complete tapering success for corticosteroids, MTX/leflunomide, and tofacitinib, respectively.
- In subjects with sJIA: achieving "Absence of Fever", defined as absence of fever due to sJIA in the week preceding the assessment at each visit.
- In subjects with Enthesitis Related Arthritis (ERA): Change from baseline in the Tender Entheseal Assessment (TEA), Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at various visits.
- In subjects with psoriatic arthritis (PsA): Change from baseline in body surface area (BSA) affected by psoriasis and Physician's Global Assessment (PGA) of psoriasis at various visits.

For details of endpoint calculation, please see Appendix 1.1 to Appendix 1.11. For details of baseline definition, please see Section 3.4.1.

3.3. Exploratory Endpoints

- Plasma concentration time data for tofacitinib will be analyzed to characterize the PK in this subject population. Exposure-response relationship will be explored for various efficacy and safety endpoints after long-term exposure of tofacitinib.

3.4. Baseline Variables

3.4.1. Definition of Baseline

Baseline will be defined in the following way for all statistical analyses except for JIA ACR disease flare, and safety monitoring and discontinuation:

- First determine the number of off-study days (enrollment gap) between the last visit date in the qualifying study and the first visit date in this extension study.
- If the gap is ≤ 14 days, the baseline value will come from the baseline value of the qualifying study, if available. If it is not available, the baseline value will be missing.
- If the gap is > 14 days, use the following decision tree to determine which baseline value, from the qualifying study or from this extension study, will be utilized in the analyses.

Qualifying Study Baseline Available [a]	Extension Study Baseline Available [b]	Baseline Value for Use in Analyses, if Gap > 14 days
No	No	No Baseline (Missing)
No	Yes	Extension Study
Yes	No	Qualifying study
Yes	Yes	Extension study

[a] The baseline values from the qualifying study with a randomized withdrawal design (i.e., A3921104 and A3921165) will come from the open-label period baseline.

[b] The baseline values from this extension study will come from 1) separate screening and baseline visits after EOS visit of the qualifying study, 2) a combined screening/baseline visit after EOS visit, or 3) a screening/baseline visit combined with the EOS visit. More specifically, extension study baseline will be the last non-missing assessment on or before Day 1 and prior to first dose of study drug administration in this extension study. Only data collected in the extension study database will be used. If a baseline value is not available by design (i.e., not planned to be collected at screening or baseline visit according to the protocol), extension study baseline availability will be "No" in the above decision tree.

For JIA ACR disease flare, baseline values will be from Month 3 visit of this extension study regardless of the gap calculated above.

For baseline definitions for use in safety monitoring and discontinuation, please see A3921145 protocol Appendix 8.

3.4.2. Baseline Disease Characteristics

For details of baseline definition, please see Section 3.4.1.

- Baseline CHAQ Disability Index
- Baseline CHAQ Discomfort Index
- Baseline CHAQ Parent Assessment of Overall Well-Being
- Baseline JADAS-27 CRP and JADAS-27 ESR
- Baseline number (%) of subjects with JADAS-27 CRP/ESR inactive disease, minimal disease activity, low disease activity, moderate disease activity and high disease activity, respectively
- Baseline number of joints with active arthritis
- Baseline number of joints with limitation of motion
- Baseline number of swollen joints
- Baseline number of painful/tender joints
- Baseline physician global evaluation of disease activity
- Baseline duration of morning stiffness
- Baseline ESR
- Baseline CRP
- Baseline number (%) of subjects who were Rheumatoid Factor positive (RF+) and negative (RF-)
- Baseline number (%) of subjects who were Antinuclear Antibodies positive (ANA+) and negative (ANA-)
- In subjects with ERA: baseline Tender Entheseal Assessment (TEA), baseline Modified Schober's Test, baseline Overall Back Pain, and baseline Nocturnal Back Pain
- In subjects with PsA: baseline %BSA and baseline PGA of Psoriasis

- In subjects with sJIA: baseline number (%) of subjects with fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy

3.5. Safety Endpoints

See Section 3.1.

4. ANALYSIS SETS

4.1. Full Analysis Set (FAS)

The full analysis set (FAS) will include all enrolled subjects with at least one dose of tofacitinib during this study.

4.2. Per Protocol Analysis Set

Not planned.

4.3. Safety Analysis Set (SAS)

The safety analysis set (SAS) will include all enrolled subjects with at least one dose of tofacitinib during this study. SAS is the same as FAS in this study.

4.4. Other Analysis Sets

The sJIA1 analysis set consists all subjects in FAS with systemic JIA (sJIA). Both sJIA subjects from index studies A3921104 and A3921165 will be included in the sJIA1 analysis set.

The sJIA2 analysis set is a subset of sJIA1 analysis set. Only sJIA subjects from index study A3921165 will be included.

The pJIA analysis set consists all subjects in FAS with polyarticular course JIA (pJIA, i.e., extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features). The pJIA analysis set will not include subjects enrolled from index study A3921165.

The ERA analysis set consists all subjects in FAS with enthesitis-related arthritis (ERA).

The PsA analysis set consists all subjects in FAS with psoriatic arthritis (PsA).

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There are no hypotheses since this study is an open--label single--arm long-term follow--up study with the primary and secondary objectives achieved through descriptive statistics.

Decision rules are not applicable since there are no formal hypotheses.

5.2. General Methods

In general, descriptive statistics will include number of subjects evaluated, number and percent for binary variables, and mean, standard deviation, minimum, 1st, 2nd (median) and 3rd quartiles and maximum for continuous variables. Graphics will be generated if needed.

5.3. Methods to Manage Missing Data

Missing data will not be imputed, and all analyses will be based on available data except Tanner Stage assessment and missing joint assessment. For Tanner Stage assessment, once a subject has reached the highest stage of development (Stage 5) then that score will be carried forward for the remainder of the study. More specifically, any missing Tanner Stage assessment after a Stage 5 score will be "imputed" with Stage 5, up to the next non-missing Tanner Stage assessment prior to study discontinuation. For missing joint assessment, the imputation method is provided in Appendix 1.2

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

The primary endpoints are standard laboratory safety data, adverse event (AE) reports, body weight, height and tanner stages. The Safety Analysis Set (SAS) will be used for analysis. For some endpoints, e.g., overall AE summary and AEs by SOC and PT, analyses will also be performed in sJIA2 analysis set and any additional summaries will be detailed in the programming plan.

All the safety data, including the following, will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations by visit:

- Adverse events will be summarized according to Pfizer standards.
- Safety laboratory tests will be summarized according to Pfizer standards.
- Subjects meeting certain cutoffs will be summarized for the following parameters: neutrophil counts, lymphocyte counts, serum creatinine levels, liver tests, lipid levels, hemoglobin.
- Subjects meeting discontinuation and monitoring criteria (see Protocol Appendix 8) will be summarized.
- Serious infections will be summarized.
- Incidence rate will be calculated for AEs of special interest. See Section 6.6 for details.
- For pubertal development as measured by Tanner Stage, a shift table of Tanner Stages from baseline to each post-baseline visit will be constructed by age group (2 to <6 years, 6 to <12 years, and 12 years or older) for males and females separately. The percentages in the shift table will be based on the number of subjects with available tanner stage data at both baseline and the post-baseline visit of interest.

- For assessment of growth as measured by body weight and height, a table of descriptive statistics for body weight and height standardized Z-scores (actual values and changes from baseline) at each visit will be constructed by age group (2 to <6 years, 6 to <12 years, and 12 years or older) for males and females separately.

  Height (weight) Z-score is calculated using the following formulation:

$$Z = \frac{(X/M)^L - 1}{LS}, L \neq 0$$

  Or

$$Z = \ln(X/M)/S, L = 0$$

  where X is the physical measurement (e.g., height, weight) and L, M, and S are the values from standardized growth charts provided by the US Centers for Disease Control website (http://www.cdc.gov/GrowthCharts/) by gender for children from birth to 240 months. The Z-score cannot be calculated if age >240 months.

6.2. Secondary Endpoints

All efficacy endpoints are secondary and listed in Section 3.2. Table 2 summarizes the analysis sets to be used in the analysis of each efficacy endpoint.

The secondary efficacy endpoints will be summarized using descriptive statistics by visit for the binary and continuous endpoints respectively. The percent (for the binary endpoints) and mean change (for the continuous endpoints) over time and associated standard errors will be plotted for analyses in sJIA1, sJIA2 and pJIA analysis sets (see Table 2).

The binary endpoints are JIA ACR responses, occurrence of JIA ACR disease flare, JIA ACR clinical inactive disease status and clinical remission, occurrence of JADAS minimum disease activity and inactive disease, eligibility of tapering, partial tapering success and complete tapering success for corticosteroids, MTX/leflunomide, and tofacitinib, absence of fever for sJIA subjects at each visit. Number, frequency, percent and the associated standard error will be presented for binary variables. JIA ACR disease flare will only be summarized for those who have reached Month 3 Visit of this extension study.

The continuous endpoints are change from baseline in physician global evaluation of disease activity, number of joints with active arthritis, number of joints with limitation of motion, CRP, ESR, CHAQ, JADAS-27 CRP, JADAS-27 ESR at each visit. Number, mean, standard deviation, standard error of the mean, median, quartiles, minimum, and maximum will be presented for continuous variables.

For ERA subjects, change from baseline in TEA, Modified Schober's Test, Overall Back Pain, Nocturnal Back Pain at each visit will be summarized as continuous variables.

For PsA subjects, change from baseline in BSA affected by psoriasis, PGA of psoriasis at each visit will be summarized as continuous variables.

For ESR and any efficacy endpoint summaries involving ESR, all ESR data points including those collected with expired/non-standard ESR kits will be used for analysis. Supportive analyses will be performed to evaluate the impact of expired/non-standard ESR kits (see Section 6.2.1).

For CHAQ and any efficacy endpoint summaries (i.e., JIA ACR responses, JIA ACR flare, and JADAS) involving CHAQ, subjects with invalid CHAQ measurements will be excluded for the visits where these invalid measurements were made. Examples of invalid CHAQ measurements include:

- incorrectly translated CHAQ data
- CHAQ data collected remotely over the phone
- CHAQ completed by the subject instead of the parent/legal guardian

Table 2. Analysis Sets for Each Efficacy Endpoint

		sJIA1*	sJIA2*	pJIA*	ERA	PsA
Efficacy endpoints defined for all subjects						
	Change from baseline (CFB) in CRP and ESR	Y	Y	Y	Y	Y
	CFB in physician global evaluation of disease activity	Y	Y	Y	Y	Y
Joint assessment	CFB in number of joints with active arthritis	Y	Y	Y	Y	Y
	CFB in number of joints with limitation of motion	Y	Y	Y	Y	Y
CHAQ	CFB in CHAQ Disability Index	Y	Y	Y	Y	Y
	CFB in CHAQ Discomfort Index	Y	Y	Y	Y	Y
	CFB in CHAQ Parent's Global Assessment of Overall Wellbeing	Y	Y	Y	Y	Y
JIA ACR	JIA ACR 30/50/70/90/100 response	Y	Y	Y	Y	Y
	JIA ACR disease flare after Month 3	Y	Y	Y	Y	Y
	JIA ACR Clinical Inactive Disease	Y	Y	Y	Y	Y
	JIA ACR Clinical Remission	Y	Y	Y	Y	Y
JADAS-27 CRP & JADAS-27 ESR	Change from baseline	Y	Y	Y	Y	Y
	JADAS minimum disease activity	Y	Y	Y	Y	Y
	JADAS inactive disease	Y	Y	Y	Y	Y
Tapering for corticosteroids, MTX/leflunomide and tofacitinib, respectively	Achieving eligibility of tapering	Y	Y	Y	Y	Y
	Achieving partial tapering success	Y	Y	Y	Y	Y
	Achieving complete tapering success	Y	Y	Y	Y	Y
Efficacy endpoints defined for specific subtypes						
In subjects with sJIA	Achieving "Absence of Fever"	Y	Y	NA	NA	NA
In subjects with ERA	CFB in TEA	NA	NA	NA	Y	NA
	CFB in Modified Schober's Test	NA	NA	NA	Y	NA
	CFB in Overall Back Pain	NA	NA	NA	Y	NA
	CFB in Nocturnal Back Pain	NA	NA	NA	Y	NA
In subjects with PsA	CFB in BSA affected by psoriasis	NA	NA	NA	NA	Y
	CFB in PGA of psoriasis	NA	NA	NA	NA	Y

Table 2. Analysis Sets for Each Efficacy Endpoint

	sJIA1*	sJIA2*	pJIA*	ERA	PsA

* Plots will be provided for analyses in these analysis sets, except for endpoints related to tapering.

6.2.1. Supportive Analyses

Supportive analyses will be performed in order to evaluate the impact of expired/non-standard ESR kits. For endpoints that take ESR as one of the components, ESR data collected with expired/non-standard ESR kits will be excluded (i.e., considered missing) and descriptive statistics will be provided by visit based on available data. Supportive analyses will be done in sJIA1, sJIA2, pJIA, ERA and PsA, separately.

- The following endpoints will be considered missing after excluding ESR data, which includes:
  - change from baseline in ESR
  - change from baseline in JADAS-27 ESR score
  - occurrence of JADAS minimum disease activity and inactive disease calculated from JADAS-27 ESR score
  - JIA ACR clinical inactive disease status and clinical remission
- For JIA ACR responses and occurrence of JIA ACR disease flare, the response status will be determined using the available components after excluding ESR data.

The list of ESR data points to be excluded will be determined before data base release.

6.3. Exploratory Endpoints

Plasma concentration -time data for tofacitinib will be analyzed using a nonlinear mixed effects modeling approach to characterize PK in this subject population if data is collected from ≥40% of the subjects. Subjects' current weight will be used as one of the primary covariates for CL/F and V/F in the model to characterize body weight mediated changes in CL/F within a subject. Relationship between various measures of systemic exposure of tofacitinib (e.g., observed or model predicted trough or 2-hour post-dose concentrations) and efficacy/long-term safety outcomes may be explored using appropriate methodology. Details will be captured in a separate Population Modeling Analysis Plan (PMAP).

6.4. Subset Analyses

Efficacy and safety analyses in sJIA1 analysis subset, sJIA2 analysis set, pJIA analysis subset, ERA analysis subset and PsA analysis subset are discussed in Sections 6.1 and 6.2.

6.5. Baseline and Other Summaries and Analyses

Baseline disease characteristics are listed in Section 3.4.2.

For variables defined specifically in subjects with ERA and PsA, ERA analysis sets and PsA analysis set will be used for baseline summaries, respectively.

For variables that are defined in all subjects, baseline summaries will be provided for FAS, and also for sJIA1 analysis set, sJIA2 analysis set, pJIA analysis set, ERA analysis set and PsA analysis set.

6.6. Safety Summaries and Analyses

Please see Section 6.1 for descriptive summaries of safety endpoints.

In addition, the Incidence Rates (IRs) of adverse events specified in the table below will be calculated.

Treatment emergent adverse events (TEAEs)
Serious adverse events (SAEs)
Adverse events (AEs) leading to discontinuation from study
All-cause deaths
All infections
Serious infections (SIs)
All herpes zoster (HZ, from the clinical database and adjudicated[a] events)
Adjudicated tuberculosis (TB)[a]
Adjudicated opportunistic infections (OIs)[a]
Adjudicated OIs excluding TB[a]
Adjudicated OIs excluding TB and HZ[a]
Hematologic events (anaemia, neutropenia, lymphopenia, and thrombocytopenia, respectively)
Adjudicated malignancy excluding non-melanoma skin cancer (NMSC)[a]
Adjudicated NMSC[a]
Adjudicated lymphoma[a]
Adjudicated major adverse cardiovascular events (MACE)[a,b]
Adjudicated deep vein thrombosis (DVT)[a]
Adjudicated pulmonary embolism (PE)[a]
Adjudicated venous thromboembolism (VTE) (i.e., adjudicated DVT or adjudicated PE)[a]
Arterial thromboembolism (ATE, from the clinical database and the adjudicated[a] events)
Thromboembolism (TE) (i.e., adjudicated DVT[a], adjudicated PE[a], or ATE)
Adjudicated drug-induced liver injury (DILI)[a] and other hepatic events[c]
Renal events[d]
Adjudicated gastrointestinal perforations[a]
Adjudicated interstitial lung disease (ILD)[e]
Adjudicated macrophage activation syndrome (MAS)[a], applicable to subjects with sJIA only.

Abbreviations: AE = adverse event; ATE = arterial thromboembolism; DILI = drug-induced liver injury; DVT = deep vein thrombosis; GI = gastrointestinal; HZ = herpes zoster; ILD = interstitial lung disease; MACE = major adverse cardiovascular events; MAS = macrophage activation syndrome; MedDRA = Medical Dictionary for Regulatory Activities; NMSC = non-melanoma skin cancer; OI = opportunistic infection; PE = pulmonary embolism; SAE = serious adverse event; SI = serious infection; SMQ = Standardised MedDRA Queries; TEAE = treatment emergent adverse event; TB = tuberculosis; TE = thromboembolism; VTE = venous thromboembolism.

a. Adjudicated by Adjudication Committees independent and external to Pfizer.
b. Components: cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
c. Including SMQs: Hepatic failure, fibrosis, and cirrhosis, and other liver damage-related conditions; and Hepatitis, non-infectious.
d. Including Acute renal failure SMQ.
e. Adjudicated by an internal review committee.

Incidence Rates (IRs) will be calculated and presented in 100 subject-years and defined as follows:

> IR = 100 * Number of Unique Subjects with Event during the Risk Period (RP) / Sum of Event Exposures for all Subjects (Subject-Years of Exposure)

The numerator of the IR will include subjects counted only once as soon as they experience a first event during their individual risk period (RP) defined below.

The denominator will be the sum of the times to event for those who experience an event during the risk period and the lengths of risk periods for those who do not experience an event. If a subject experiences multiple instances of the same event, the time to first occurrence of the event will be considered.

In general, a subject is considered at risk to experience an AE while on tofacitinib treatment and within 28 days of stopping tofacitinib treatment. Thus, the risk period extends from the subject's first dose of tofacitinib up to the date of last dose of tofacitinib + 28 days.

For the final analysis, the RP is defined as:

> RP = min(last dose date + 28 days, last contact date) – first dose date + 1 day.
>
> The last contact date will be the maximum of (AE start date, AE stop date, last study visit date, withdrawal date). If a subject is dead, the last contact date will be the death date.

For an interim analysis with a data cutoff date, the RP is defined as:

> RP = min(last dose date + 28 days, last contact date, data cutoff date) – first dose date + 1 day.

95% CI (corresponding to α=0.05) for this IR will be calculated based on the assumption that the actual count of cases (i.e., unique subjects with events) arises from an exact Poisson distribution. The approach used in Daly (1992)[1] describing the calculation of exact confidence limits will be used. If *x* denotes the actual number of subjects with events, the (1

– α)×100% confidence limit, x_L the lower confidence limit and x_U the upper confidence limit, then the following formula yields values for x_L and x_U,

When $x > 0$,

$$x_L = 0.5 * \chi^2(\alpha/2; 2x) \text{ and } x_U = 0.5 * \chi^2(1- \alpha/2; 2x+2),$$

When $x = 0$,

$$x_L = 0 \text{ and } x_U = 0.5 * \chi^2(1- \alpha/2; 2x+2).$$

In the above notation, $\chi^2(p; n)$ represents the p^{th} quantile of the chi-square distribution with n degrees of freedom. Once x_L and x_U are obtained, they are to be adjusted for the at-risk population per 100 subject-years by multiplying by 100.

In addition, all adjudicated events will be listed.

Additionally, Potential Hy's Law Cases, defined as patients with AST or ALT ≥3 x the upper limit of normal (ULN) concurrent with a total bilirubin ≥2 x ULN, will be summarized.

6.7. Additional Analyses Depicting COVID-19 Pandemic Impact

- An anchor date will be used as a start date for COVID-19 pandemic related periods in analyses.
    - For China sites, the date COVID-19 was identified as the causative agent of outbreak in Wuhan by the China Center for Disease Control and Prevention (January 9, 2020) will be used as the anchor date for COVID-19 pandemic.
    - For non-china sites, the date the World Health Organization designated COVID-19 as a global pandemic (March 11, 2020) will be used as the anchor date.
- The date the World Health Organization declared COVID-19 over as a global health emergency (May 5, 2023) will be used as the end date for COVID-19 pandemic related periods in analyses.
- A summary table showing visits attended both before and after the anchor date will be produced. Visit attendance will be based on physician global evaluation of disease activity data.
- A separate summary table solely for subject discontinuations related to COVID-19 pandemic, if any, will be provided.
- Protocol deviations related to COVID-19 pandemic will be summarized and listed separately. Both important and non-important PDs related to COVID-19 pandemic will be reported.
- COVID-19 related AEs, if any, will be reported separately.

- A summary table showing AEs reported both before and after the anchor date will be produced. This summary will consider windows of equal duration before and after the anchor date.

7. INTERIM ANALYSES

There are no planned formal interim analyses. Interim analyses may be performed for study monitoring for internal decision making, regulatory purposes or for planned publications.

The final analysis will be performed following the official database release.

This study is not randomized, and all treatments are open-labeled.

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9. APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. The JIA Core Set Variables

The JIA ACR Response and Flare Criteria assessment (Giannini 1997)[2] is a derived measurement of the 6 components of the JIA core set variables, which includes:

- Physician global evaluation of disease activity.
- Number of joints with active arthritis.
- Number of joints with limited range of motion.
- Parent/legal guardian/subject evaluation of overall well-being (from the CHAQ).
- Functional ability (Disability Index from the CHAQ).
- ESR.

The ACR definition of active arthritis is any joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity.

Appendix 1.2. The JIA Joint Counts

For swollen joints, painful/tender joints and joints with limitation of motion, respectively, before calculating the joint count, the following pre-processing step for each joint should be performed:

- If a joint receives an intra-articular injection (either at Baseline or post-baseline visits), set the joint status to “Present” on or after the date of injection.
- If the site of injection is not recorded and/or cannot be identified, the joint assessment on the CRF (either “Present” or missing) will be used.

After this pre-processing, a joint assessment that is missing is considered “absent”, thus a good joint. To calculate the number of joints with active arthritis and the number of joints with limited range of motion, only “present” joints will be taken into account.

Appendix 1.3. JIA American College of Rheumatology (ACR) Response

The assessments using JIA ACR 30, 50, 70, 90 and 100 will be performed. Other responder criteria may be assessed if appropriate. The JIA ACR 30, 50, 70, 90, 100 response criteria (Giannini 1997)[2] are as follows: 3 out of 6 JIA core set variables improved ≥30%, 50%, 70%, 90%, 100%, respectively, with no more than 1 out of 6 JIA core set variables worsened by ≥30%. Only ESR will be used to calculate ACR responses.

If the value in any of the components at a timepoint is missing, the component variables that are not missing will be used to determine the response status. As a general principle, if there are sufficient non-missing components to determine whether the JIA ACR endpoint is a response or non-response, then JIA ACR endpoint is not missing, else if the available non-missing components are not sufficient to determine the response status of JIA ACR endpoint then it is considered missing.

In order to avoid numerical difficulty, if the baseline value of any component is equal to 0, the following algorithm will be used in evaluating the percent change from baseline:

1. If change from baseline is also equal to 0, then percent change from baseline is set to be 0%;
2. If change from baseline is > 0, then percent change from baseline is set to be 999999%.

These percentages will be used to derive the JIA ACR endpoints. Change from baseline cannot be < 0 since none of the components should have negative value.

In subjects with systemic JIA, absence of fever due to sJIA in the preceding 7 days is also required (Ruperto 2012)[3]. Note that here is different from index study A3921104 protocol, where only absence of fever due to sJIA is required (no requirement of timeframe).

Appendix 1.4. Disease Flare

JIA ACR flare (Brunner 2002)[4] is defined as a worsening of 30% or more in 3 or more of the 6 variables of the JIA core set listed above, with no more than one variable improving by 30% or more. In addition, the following minimum worsening contingencies apply: if either the number of active joints or the number of joints with limited range of motion is included in the calculation of "flare" then there must be a worsening of at least two joints. If the Physician's or parent/legal guardian global rating scores are used in the definition of "flare" then there must be a worsening of at least 2 units on the 10-unit scales. If the ESR is used in the definition of "flare" then the second value for the ESR used in the calculation must be above the upper limit of normal for the ESR.

In addition, for subjects with sJIA from A3921104 and A3921165, a disease flare may also constitute a recurrence of fever due to sJIA of >38°C/100.4°F (oral) or >101.4°F/38.6°C (rectal) on 2 or more consecutive days (Ruperto 2012)[3]. Note that here is different from index study A3921104 protocol, where 2 or more consecutive days for fever was not required.

Missing component handling will be the same as that for JIA ACR responses (See Appendix 1.3).

Appendix 1.5. JIA ACR Clinical Inactive Disease Status Determination and Clinical Remission Criteria

The American College of Rheumatology (ACR) JIA Clinical Inactive Disease and Clinical Remission (Wallace 2011)[5] criteria is defined as follows:

The Clinical Inactive Disease:

The Clinical Inactive Disease Status Determination assessment is a derived measurement and defined as follows: which includes:

- No joints with active arthritis.
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.
- No active uveitis (as defined by the SUN Working Group).
- ESR or CRP levels within normal limits in the laboratory where tested or, if elevated, not attributable to JIA. There will be two endpoints: Clinical Inactive Disease Status defined by ESR and Clinical Inactive Disease Status defined by CRP.
- Physician global evaluation of disease activity score of 'best possible' on the scale used.
- Duration of morning stiffness of ≤15 minutes.

Since uveitis exam will be performed annually, for the purpose of determining JIA ACR Inactive Disease status, the last uveitis assessment result will be carried forward up to the next non-missing uveitis assessment prior to study discontinuation.

After the pre-processing of uveitis assessment, if any of the components is missing, the components that are not missing will be used to determine the Clinical Inactive Disease Status as follows:

- Inactive disease: all components must be present (non-missing) and meet all conditions.
- Active disease: at least one component is present (non-missing) and does not meet the condition.
- Not determined: any other scenarios.

Clinical Remission on Medications:

- Inactive disease as defined above for 6 months (24 weeks) continuously while on medications.

Clinical inactive disease and clinical remission status will be based on the investigator's assessment of the above components.

Note that when calculating clinical remission, only inactive disease in this study will be included in the 24 weeks count.

Appendix 1.6. Juvenile Arthritis Disease Activity (JADAS-27 CRP and JADAS-27 ESR) Score

JADAS-27 CRP and JADAS-27 ESR score consists of four components (Consolaro 2009, Bazso 2009, Nordal 2012) [6,10,11]:

- Physician global assessment of disease activity;
- Parent/legal guardian/subject global assessment of Child well-being (from the CHAQ);
- Number of joints with active disease (27 joint assessment);
- CRP or ESR.

The 27 joints used here are bilateral Elbow, Wrist, MCP 1-3, PIP 1-5, Hip, Knee and Ankle, plus Cervical Spine.

The CRP value will be normalized to a 0 – 10 scale according to the following formula:

$$(\text{CRP (mg/L)} - 2.87)/10$$

Before calculation, CRP values <2.87 mg/L will be converted to 2.87 and CRP values >102.87 mg/L will be converted to 102.87. The value 2.87 (mg/L) here is the upper bound of the reference range provided by the lab.

The ESR value will be normalized to 0 – 10 scale as below:

$$(\text{ESR} - 20)/10$$

Before calculation, ESR values <20 mm/h will be converted to 20 and ESR values >120 mm/h will be converted to 120.

JADAS-27 CRP/ESR score will be calculated as the simple linear sum of the scores of its 4 components, which yields a global score of 0 – 57 for the JADAS-27 CRP/ESR score.

If any of the components is missing, the JADAS-27 CRP/ESR score will be considered missing.

Appendix 1.7. JADAS-27 High Disease Activity, Moderate Disease Activity, Low Disease Activity, Minimal Disease Activity and Inactive Disease

The cutoff values in the JADAS-27 that correspond to inactive disease and minimal/low/moderate/high disease activity (Consolaro 2012, Consolaro 2014, Consolaro 2016)[7,8,9] are defined as follows:

Polyarthritis (>4 active joints) at baseline:

- Minimal Disease Activity: ≤3.8.
  - Inactive Disease: ≤1.0.
  - Low Disease Activity: >1.0 – ≤3.8.
- Moderate Disease Activity: >3.8 – ≤8.5.
- High Disease Activity: >8.5.

Oligoarthritis (≤4 active joints) at baseline:

- Minimal Disease Activity: ≤2.0.
  - Inactive Disease: ≤1.0.
  - Low Disease Activity: >1.0 – ≤2.0.
- Moderate Disease Activity: >2.0 – ≤4.2.
- High Disease Activity: >4.2.

For JADAS-27 inactive disease and minimal/low/moderate/high disease activity for extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA, PsA and ERA subjects with >4 active joints at baseline, the cutoff values of polyarthritis will be used. For JADAS-27 inactive disease and minimal/low/moderate/high disease activity for PsA, ERA and systemic JIA subjects with ≤ 4 active joints at baseline, the cutoff values of oligoarthritis will be used.

Note that both JADAS-27 CRP and JADAS-27 ESR score will be used as cut-off values, so there will be two sets of JADAS minimum/low/moderate/high disease activity and inactive disease, one uses JADAS-27 CRP and the other uses JADAS-27 ESR.

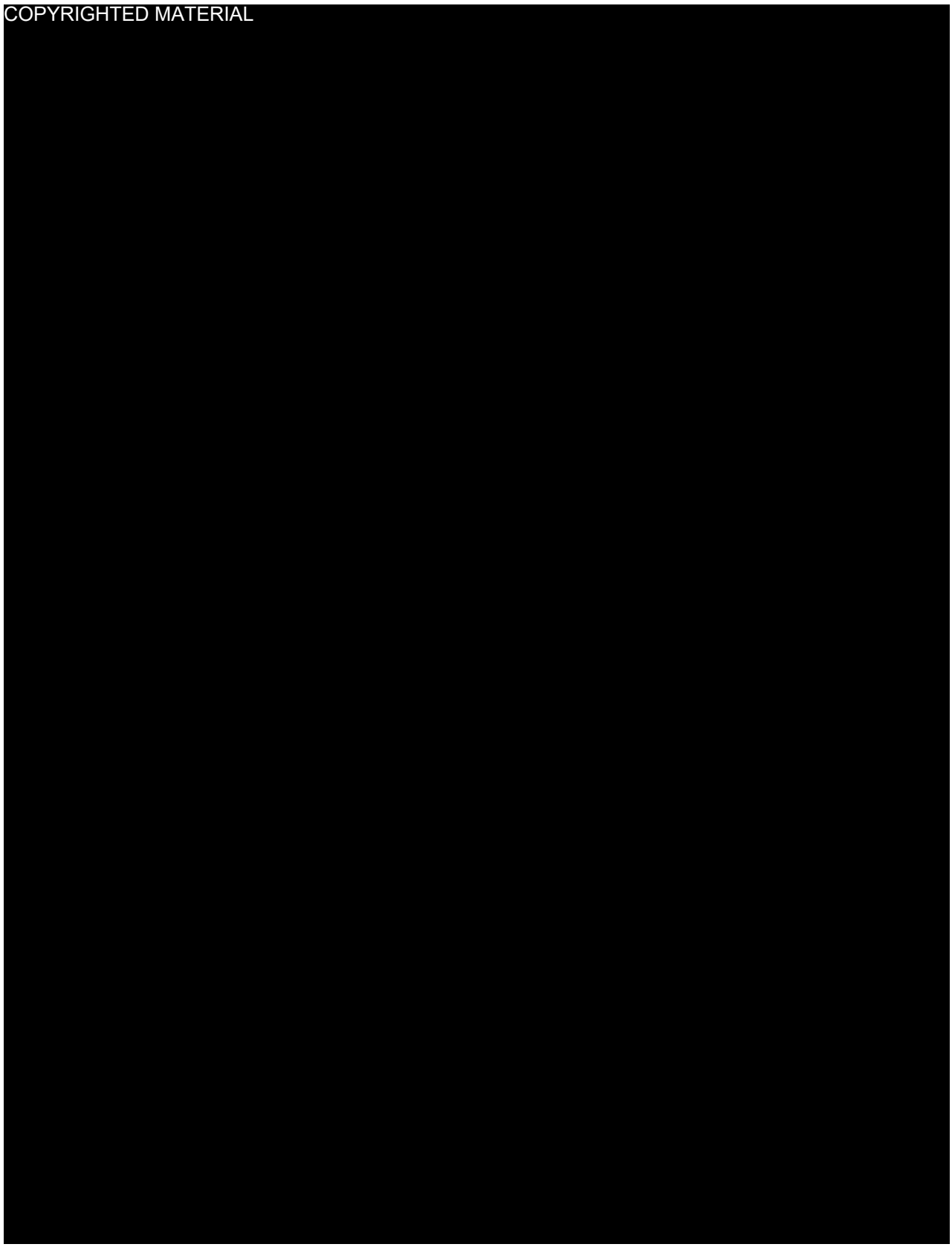
Appendix 1.8. Tapering of Corticosteroids, MTX/Leflunomide, and Tofacitinib

Data for tapering calculation will be captured in CRF. For each drug (Corticosteroids, MTX/Leflunomide, and Tofacitinib), if the subject start tapering based on investigator's judgment, the subject is considered eligible for tapering; if the subject's dose level goes down to a lower level by the end of study, the subject is considered achieving partial tapering

success; if the subject completely tapered off the drug, the subject is considered achieving complete tapering success.

- Proportion of subjects achieving eligibility of tapering = number of subjects who took the drug and started tapering/number of subjects who took the drug;
- Proportion of subjects achieving partial tapering = number of subjects who were able to undergo tapering from one dose level to a lower dose level/number of subjects who took the drug;
- Proportion of subjects achieving complete tapering = number and percentage of subjects discontinued drug completely/number of subjects who took the drug.

Appendix 1.9. CHAQ Responses



Appendix 1.10. ERA: Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain Responses

Tender Entheseal Assessment

Following anterior/posterior and left/right joint assessment, the investigator will enter one of the following codes for each enthesis on the appropriate CRF. Palpation should be performed per standard practice (e.g., using fingertips) for this assessment.

Y = Any tenderness upon firm palpation over the indicated enthesis

N = No tenderness upon firm palpation over the indicated enthesis

Number of joints with any tenderness will be counted for the report of Tender Entheseal Assessment.

Modified Schober's Test (Macrae 1969, Moll 1971)[14, 15]

With the subject standing erect and with feet together, a line joining the posterior superior iliac spines (the dimples of Venus) is used as a landmark for the lumbosacral junction. A mark is made 5 cm below and 10 cm above the lumbosacral junction. With the subject in maximum forward flexion with the knees straight, the investigator will measure the distance between the two marks in centimeters. The full measurement between the two lines will be recorded to the nearest tenth of a centimeter (e.g., 15.2 cm) on the appropriate CRF.

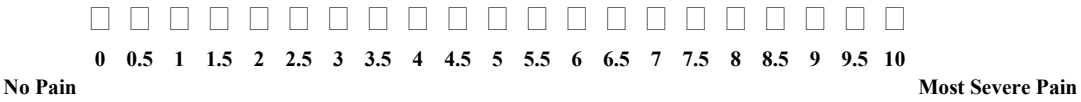
Overall Back Pain and Nocturnal Back Pain

Overall back pain (at any time) and nocturnal back pain will be measured on a 21-circle visual analog scale (VAS).

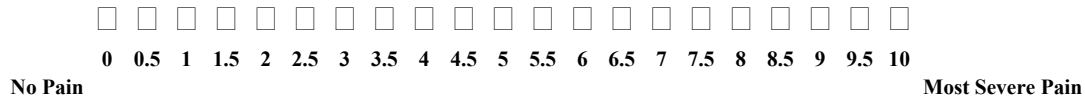
The parent/legal guardian/subject (if at least 14 years of age and able to complete correctly and consistently) will be asked to fill one circle on the scale shown below in response to the following questions:

Overall Back Pain (Please fill a circle)

What is the amount of back pain at any time that your child experienced in the past week?



Nocturnal Back Pain (Please fill a circle) What is the amount of back pain at night that your child experienced in the past week?



Appendix 1.11. PsA: Body Surface Area (BSA) and Physician's Global Assessment (PGA) of Psoriasis

Subjects with psoriatic arthritis (PsA) will undergo additional efficacy assessments, including assessment of body surface area (BSA) affected by Psoriasis and Physician's Global Assessment (PGA) of psoriasis (Horneff 2014) [16].

Body Surface Area (BSA)

BSA will be measured as the percentage of BSA affected by psoriasis using the palm method; the subject's palm will be used for the calculation.

One (1) of the subject's palm to PIP and thumb equals 1% of BSA.

Head and Neck = 10% (10 palms)

Upper extremities = 20% (20 palms)

Trunk (axillae and groin) = 30% (30 palms)

Lower extremities (buttocks) = 40% (40 palms)

Total BSA = 100% (100 palms)

Based on the above, the Physician's Assessment of Total BSA affected by psoriasis will be estimated using the following formula:

Region of the Body	Number of Palms Within the Region Affected by Psoriasis
Head and Neck	
Upper extremities	
Trunk (including the axillae and groin)	
Lower extremities (including the buttocks)	
Physician's Assessment of Total BSA Affected by Psoriasis (addition of the individual regions):	%

Physician's Global Assessment (PGA) of Psoriasis

The PGA of psoriasis is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions are graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales is then divided by 3 to obtain the final PGA of psoriasis score.

Please circle one response each for induration, erythema, and scaling:	
Induration (I) (averaged over all lesions): 0 = no evidence of plaque elevation 1 = minimal plaque elevation - 0.5 mm 2 = mild plaque elevation - 1 mm 3 = moderate plaque elevation - 1.5 mm 4 = marked plaque elevation - 2 mm 5 = severe plaque elevation - 2.5 mm or more	**Erythema (E)** (averaged over all lesions): 0 = no evidence of erythema, hyper pigmentation may be present 1 = faint erythema 2 = light red coloration 3 = moderate red coloration 4 = bright red coloration 5 = dusky to deep red coloration
Scaling (S) (averaged over all lesions): 0 = no evidence of scaling 1 = minimal; occasional fine scale over less than 5% of the lesion 2 = mild; fine scale predominates 3 = moderate; course scale predominates 4 = marked; thick, non-tenacious scale predominates 5 = severe; very thick tenacious scale predominates	

Add I + E + S = _____ / 3 = _____ (Total Average)

- ☐ (0) Clear, except for residual discoloration
- ☐ (1) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 1**
- ☐ (2) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 2**
- ☐ (3) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 3**
- ☐ (4) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 4**
- ☐ (5) Majority of lesions have individual scores for [(I + E + S) / 3] that **averages 5**

Note: Scores should be rounded to the nearest whole number:

If total average ≤1.49, score = 1

If total average ≥1.50, score = 2

Appendix 1.12. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy variables, and for any safety displays that display by visit. If more than one observation from the same subject falls into the same visit window, the value closest to the targeted day will be used as the observation for that visit. If there are two days having the same distance from target day, the earlier day will be used. All observations will, however, be included in the listings.

Visit Label	Target Day	Definition [Day window]
Baseline	Day 1	Day 1
Month 1	Day 30	Days 2-60
Month 3	Day 90	Days 61-135
Month 6	Day 180	Days 136-225
Month 9	Day 270	Days 226-317
Month 12	Day 360+5=365	Days 318-410
Month 15	Day 450+5=455	Days 411-500
Month 18	Day 540+5=545	Days 501-590
Month 21	Day 630+5=635	Days 591-683
Month 24	Day 720+10=730	Days 684-775
Month 27	Day 810+10=820	Days 776-865
Month 30	Day 900+10=910	Days 866-955
Month 33	Day 990+10=1000	Days 956-1048
Month 36	Day 1080+15=1095	Days 1048-1140
Month 39	Day 1170+15=1185	Days 1141-1230
Month 42	Day 1260+15=1275	Days 1231-1320
Month 45	Day 1350+15=1365	Days 1321-1413
Month 48	Day 1440+20=1460	Days 1414-1505
Month 51	Day 1530+20=1550	Days 1506-1595
Month 54	Day 1620+20=1640	Days 1596-1685
Month 57	Day 1710+20=1730	Days 1686-1778
Month 60	Day 1800+25=1825	Days 1779-1870
Month 63	Day 1890+25=1915	Days 1871-1960

Visit Label	Target Day	Definition [Day window]
Month 66	Day 1980+25=2005	Days 1961-2050
Month 69	Day 2070+25=2095	Days 2051-2143
Month 72	Day 2160+30=2190	Days 2144-2235
Month 75	Day 2250+30=2280	Days 2236-2325
Month 78	Day 2340+30=2370	Days 2326-2415
Month 81	Day 2430+30=2460	Days 2416-2508
Month 84	Day 2520+35=2555	Days 2509-2600
Month 87	Day 2610+35=2645	Days 2601-2690
Month 90	Day 2700+35=2735	Days 2691-2780
Month 93	Day 2790+35=2825	Days 2781-2873
Month 96	Day 2880+40=2920	Days 2874-2965
Month 99	Day 2970+40=3010	Days 2966-3055
Month 102	Day 3060+40=3100	Days 3056-3145
Month 105	Day 3150+40=3190	Days 3146-3238
Month 108	Day 3240+45=3285	Days 3239-3330
Month 111	Day 3330+45=3375	Days 3331-3420
Month 114	Day 3420+45=3465	Days 3421-3510
Month 117	Day 3510+45=3555	Days 3511-3603
Month 120[a]	Day 3600+50=3650	≥ Days 3604

a: Additional visits may be added depending on the actual total duration of the study.

For the summary of Tanner Stage, the following visit windows will be used.

Visit Label	Target Day	Definition [Day window]
Baseline	Day 1	Day 1
Month 12	Day 360+5=365	Days 2-547
Month 24	Day 720+10=730	Days 548-912
Month 36	Day 1080+15=1095	Days 913-1277
Month 48	Day 1440+20=1460	Days 1278-1642
Month 60	Day 1800+25=1825	Days 1643-2007
Month 72	Day 2160+30=2190	Days 2008-2372
Month 84	Day 2520+35=2555	Days 2373-2737
Month 96	Day 2880+40=2920	Days 2738-3102
Month 108	Day 3240+45=3285	Days 3103-3467
Month 120[a]	Day 3600+50=3650	≥ Days 3468

a: Additional visits may be added depending on the actual total duration of the study.

Appendix 1.13. Protocol Deviations

While protocol deviations will be listed in the clinical study report, none will form part of statistical analyses since no per protocol analyses are planned.

Appendix 2. List of Abbreviations

Abbreviation	Term
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	arterial thromboembolism
BSA	body surface area
CFB	change from baseline
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CL/F	oral clearance
COVID-19	corona virus disease 2019
CRF	case report form
CRP	C-reactive protein
DILI	drug induced liver injury
DMARD	disease modifying antirheumatic drug
DVT	deep vein thrombosis
EMA	European Medicines Agency
EOS	end of study
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
EU VHP	EU Voluntary Harmonisation Procedure
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GI	gastrointestinal
HZ	herpes zoster
IFN	interferon
IL	interleukin
ILD	interstitial lung disease
IR	incidence rate
JADAS	Juvenile Arthritis Disease Activity Score
JAK	janus kinase
JIA	juvenile idiopathic arthritis
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MAS	macrophage activation syndrome
MCP	metacarpophalangeal
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NMSC	nonmelanoma skin cancer
OI	opportunistic infection
PD	Protocol deviation

Abbreviation	Term
PE	pulmonary embolism
PGA	Physician's Global Assessment
PIP	proximal interphalangeal
pJIA	polyarticular course juvenile idiopathic arthritis
PK	pharmacokinetic(s)
PMAP	population modeling analysis plan
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RF+	rheumatoid factor positive
RF-	rheumatoid factor negative
RP	risk period
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SI	serious infection
sJIA	systemic juvenile idiopathic arthritis
SMQ	standardised MedDRA queries
SOC	system organ class
SOP	standard operating procedure
SUN	Standard Uveitis Nomenclature
TB	tuberculosis
TE	thromboembolism
TEA	tender entheseal assessment
TEAE	treatment-emergent adverse event
TyK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VTE	venous thromboembolism